The Relation Between Multiple Sleep Latency Test Findings and the Frequency of Apneic Events in REM and Non-REM Sleep*

Ronald D. Chervin, MD, MS; and Michael S. Aldrich, MD

Study objectives: A recent study of 34 patients with mild obstructive sleep apnea syndrome (OSAS) suggested that the number of apneas and hypopneas per hour of sleep (apnea/hypopnea index [AHI]) may show a stronger correlation with sleepiness, as measured by the Multiple Sleep Latency Test (MSLT), when calculated for rapid eye movement (REM) sleep alone (AHIR) as opposed to the entire night. We sought to reexamine this possibility in a larger group of similar patients and in patients who had a wider range of OSAS severity.

Design: Retrospective and observational.

Setting: A large, accredited, academic sleep disorders center where a database of sleep study results is maintained.

Patients: We studied 1,146 persons who had polysomnography and MSLTs for clinical indications.

Results: In linear regression models, the AHI explained 11.0% of the variance in MSLT results, AHIN (AHI during non-REM sleep) explained 10.8%, and AHIR explained only 6.0% (p≤0.0001 for each). Among subjects with AHI < 10, the AHI explained 3.1% of the variance (p=0.0012), the AHIN 2.3% (p=0.0049), and the AHIR 0.2% (p=0.40). Among all subjects, the ratio AHIR/AHIN had no influence on the overall relationship between AHI and sleepiness (p=0.23).

Conclusions: We conclude that apneic events during REM and non-REM sleep probably contribute equally to sleepiness as measured by the MSLT. (CHEST 1998; 113:980-84)

Key words: Multiple Sleep Latency Test; non-REM sleep; obstructive sleep apnea syndrome; polysomnography; REM sleep; sleepiness

Abbreviations: AHI=apnea/hypopnea index, the number of apneas or hypopneas per hour of sleep; AHIN=AHI during non-REM sleep; AHIR=AHI during REM sleep; BMI=body mass index; EDS=excessive daytime sleepiness; MSL=mean sleep latency; MSLT=square root transformation of MSL; MSLT=Multiple Sleep Latency Test; NREM sleep=non-rapid eye movement sleep; OSAS=obstructive sleep apnea syndrome; REM=rapid eye movement

Patients with obstructive sleep apnea syndrome (OSAS) experience repetitive cessation or decrement in breathing during sleep, but their main complaint is often excessive daytime sleepiness (EDS). The cause of EDS in these patients, while not known for certain, is thought to involve disruption of sleep induced by apneas and hypopneas.1,2 Severity of EDS is reflected by the mean sleep latency (MSL) on the Multiple Sleep Latency Test (MSLT), which is considered the gold standard for the objective assessment of sleepiness.3 In research that includes sleep studies, the presence of OSAS and its severity are often determined by the number of apneas and hypopneas per hour of sleep (apnea/hypopnea index [AHI]). However, the AHI has not shown a strong relation to EDS as measured by the MSL. An analysis from our laboratory (n=123 patients) suggested that AHI explained 17.6% of the variance in a transformation of MSL.4 Data from another group (n=466) suggested that the number of apneas or hypopneas associated with arousal, per hour of sleep, explained 13% of the variance in MSL.1 A third study (n=100) showed a weak, if any, association between AHI and MSL5 and three other studies6,8 (n=147, 29, and 10, respectively) showed no statistically significant association.

Kass et al9 recently suggested that in contrast to the overall AHI, the AHI during rapid eye movement (REM) sleep may better predict the MSL, at least in a subset of patients—those evaluated for suspicion of OSAS but found to have an overall AHI.

*From the Department of Neurology and Sleep Disorders Center, University of Michigan Medical Center, Ann Arbor. Manuscript received May 14, 1997; revision accepted October 2, 1997.
Reprint requests: Ronald D. Chervin, MD, Sleep Disorders Center, University Hospital 8D8/702, Box 0117, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0117; email: chervin@umich.edu

980

Clinical Investigations

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21763/ on 04/28/2017
<10. Among 34 such subjects, the AHI during REM sleep (AHIR) explained 35% of the variance in MSL. The authors noted that this finding could be consistent with previous suggestions that sleepiness may result from disordered REM sleep alone. However, Kass et al did not review data for their subjects with worse sleep-disordered breathing, did not speculate why disruption of REM sleep should have a more important influence on the MSL in mild apneics than in more severe apneics, and did not compare the AHI during non-REM (NREM) sleep (AHI/N) to AHIR. In addition, in searching for a relation with MSL, Kass et al tested a number of variables (18) that was large in relation to the sample size; as a consequence, interpretation of the results is more difficult.

A particularly influential role of pathologic breathing during REM sleep would have important implications for clinical evaluations and future research. We therefore tried to confirm the hypothesis that AHIR is strongly associated with MSL. We used data collected in our laboratory during the past 8 years from 1,146 subjects; 342 had an AHI <10 and 804 had more frequent events. We also compared AHIN with AHIR and AHI.

**Materials and Methods**

**Subjects**

Results of all sleep studies performed in our laboratory since 1986 are stored on computer. Previous publications have discussed selected subjects from this database of >9,000 studies, but the 1,146 subjects described herein and the subset (n=342) with AHI <10 form unique samples that were identified as follows: All subjects had diagnostic, full-night polysomnography and MSLTs on the following day, between January 1, 1989, and February 1, 1997. For each subject, indications for polysomnography included the possibility of a sleep-related breathing disorder, and/or polysomnography demonstrated a sleep-related breathing disorder. Patients studied for suspected narcolepsy or found to have narcolepsy were excluded. Patients with other primary indications for study or other major diagnoses that cause EDS (eg, periodic limb movement disorder, idiopathic hypersomnia, or significant medical conditions such as congestive heart failure) were also excluded. Patients who had disorders related to sleep schedules, such as insufficient sleep syndrome, were included if they met all other criteria also. Patients who had no REM sleep on their polysomnogram were excluded.

**Procedures**

Nocturnal polysomnography included four EEG leads (C3-A2, Cz-A1, O1-A2, O2-A1) of the 10-20 international electrode placement system, two electro-oculographic leads (right and left outer canthii), chin and bilateral anterior tibialis surface electromyograms, two ECG leads, nasal and oral airflow, thoracic and abdominal excursions, and finger oximetry. A small fraction of the subjects also had concurrent monitoring of esophageal pressure with a water-filled catheter. Polysomnograms were generally terminated and patients awakened at 7 AM. Sleep stage scoring was performed on 30-s epochs according to standard criteria by technologists who had undergone an extensive training program and had correctly scored (as determined by two physicians board certified in sleep medicine) at least 90% of epochs in a set of reliability records. Procedures have remained equivalent in our laboratory over the past 8 years under the direction of the same medical director and chief technologist. An apnea was defined as complete cessation of airflow during sleep for at least 10 s. A hypopnea was defined as a reduction in airflow leading to either a ≥4% oxyhemoglobin desaturation, an arousal, or an awakening.

Sleepiness was assessed with MSLTs that were performed according to standard criteria and involved the same EEG, electro-oculographic, and chin electromyographic leads used for the polysomnograms. Each patient’s MSL was calculated as the mean number of epochs from “lights out” to the first epoch of stage 1 sleep; for nap attempts on which no sleep occurred, a latency of 20 min was assigned.

**Data Analysis**

Data were analyzed with a statistical software package (SAS; SAS Institute Inc; Cary, NC). Assessment of MSL for normality included calculation of skewness and kurtosis, stem-and-leaf box plots, and normal probability plots. The square root transformation of MSL (MSLRT) approximated a normal distribution better than did MSL. Linear regressions were used to model the relation between MSLRT (the outcome variable) and AHI, AHIN, and AHIR (explanatory variables). Multiple regressions were used to model the independent relation of AHIR to MSLRT, and that of AHIN to MSLRT, while controlling for the overall relation of AHIR to MSLRT in each case. Multiple regression models were also used to control potential confounding factors, including age, sex, body mass index (BMI), and date of study. The significance level was set at p<0.05.

**Results**

The 1,146 subjects were 29% female; the average subject was middle aged, was overweight, and had a moderate degree of obstructive sleep apnea (Table 1). Subjects with an AHI <10 differed significantly (p<0.0001) from those with an AHI ≥10 in the proportion that were female and in age, BMI, AHI, minimum oxygen saturation, AHIN, and AHIR. Sleep efficiency and quality were reduced (p<0.0001), as expected, in patients with higher AHIs in comparison to those with lower AHIs.

The Pearson correlation between AHIN and AHIR attained a moderate magnitude (r=0.64, p<0.0001). The mean ratio of AHIR/AHIN was 3.3 (95% confidence interval [2.9, 3.7]) among all subjects, 5.9 [4.7, 7.1] among subjects with AHI <10, and 2.2 [1.9, 2.5] among subjects with AHI ≥10. An inverse correlation among all the subjects between AHI and AHIR/AHIN (r=-0.20, p<0.0001) also indicated that subjects with lower AHIs had a larger proportion of their apneas and hypopneas in REM sleep.

In a linear regression model of the data from all
the subjects, AHI explained 11.0% of the variance in levels of sleepiness (R²=0.110, p≤0.0001, Table 2). Two nonlinear models were tested and offered little improvement in R², which was 0.116 when AHI was categorized into four levels and 0.120 when a quadratic term for AHI was added.

In two linear models, AHIN explained only 6% of the variance in MSLRT but AHIN explained 10.8%. Results were similar among the 804 subjects with AHI ≥10, but among the 342 with AHI <10, the amount of variance in sleepiness explained by AHI and AHIN was small and the amount explained by AHIR was nearly zero (Table 2).

In two multiple regression models, either AHIN and AHI or else AHIR and AHI were used as explanatory variables with sleepiness (MSLRT) as the outcome. The total amount of variance in MSLRT explained by each of these models was equivalent to that explained by AHI alone. For both models, results were similar whether data were taken from all subjects, the group with AHI <10, or the group with AHI >10: the AHIN and AHIR made no statistically significant contributions to sleepiness after controlling for AHI. Conversely, AHI made no statistically significant contribution after controlling for AHIN but still made a highly significant, independent contribution after controlling for AHIR (p≤0.0007 within each of the three groups of subjects). A multiple regression model of MSLRT on AHIN and AHIR showed that AHIN was significantly and independently associated with level of sleepiness (p≤0.006 for each group of subjects) but AHIR was not (p>0.10 for each group).

To further investigate the relative contribution to sleepiness of apneic events in REM vs NREM sleep, the ratio AHIR/AHIN was used as an additional explanatory variable in the regression of MSLRT on AHI for all the subjects. This model explained 11.1% of the variance in levels of sleepiness but the contribution of AHIR/AHIN, after accounting for the overall AHI, was nearly zero (part R²=0.001) and was not significant (p=0.23). An interaction model indicated that the lack of effect of AHIR/AHIN was not statistically different for lower or higher ranges of AHI (interaction term p=0.10).

All regression models were also tested with age, gender, BMI (available for some subjects, as indicated in Table 1), and date of the study as additional explanatory variables since these could be potential confounds of the relationships between MSLRT and AHI, AHIN, or AHIR. For example, unsuspected changes with time in scoring or patient referrals, during the 8 years of studies, could theoretically have affected both AHI and MSLRT and could have created an artificial relationship between the two variables. However, none of the relationships we have reported became statistically significant or non-significant as a result of controlling for age, gender, BMI, and date of the study, with two minor exceptions. The association between AHIR and MSLRT in subjects with an AHI ≥10 lost significance (p=0.057 instead of p≤0.0001). The effect of the interaction

Table 1—Subject Characteristics, Sleep Architecture, and Measures of Sleep Apnea*†

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>AHI&lt;10</th>
<th>AHI≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1,146</td>
<td>342</td>
<td>804</td>
</tr>
<tr>
<td>Female, %</td>
<td>29.9</td>
<td>49.7</td>
<td>21.5</td>
</tr>
<tr>
<td>Age, yr</td>
<td>45.2±13.0</td>
<td>38.9±13.0</td>
<td>47.9±12.0</td>
</tr>
<tr>
<td>BMI, kg/m²21</td>
<td>31.9±8.0</td>
<td>29.3±8.0</td>
<td>33.4±7.7</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>83.2±11.2</td>
<td>85.6±10.2</td>
<td>82.2±11.4</td>
</tr>
<tr>
<td>Percent stage 1</td>
<td>29.9±19.4</td>
<td>17.0±8.6</td>
<td>35.5±20.1</td>
</tr>
<tr>
<td>Percent stage 2</td>
<td>48.0±14.9</td>
<td>54.8±9.6</td>
<td>45.1±15.8</td>
</tr>
<tr>
<td>Percent stage 3/4</td>
<td>6.9±7.9</td>
<td>11.0±9.2</td>
<td>5.1±6.6</td>
</tr>
<tr>
<td>Percent stage REM</td>
<td>15.1±6.2</td>
<td>17.0±5.8</td>
<td>14.2±6.2</td>
</tr>
<tr>
<td>AHI</td>
<td>30.9±33.1</td>
<td>4.5±28.7</td>
<td>42.1±33.7</td>
</tr>
<tr>
<td>Min O₂¹</td>
<td>78.4±14.5</td>
<td>87.4±6.5</td>
<td>74.6±15.3</td>
</tr>
<tr>
<td>AHIN</td>
<td>29.4±94.1</td>
<td>3.3±26.6</td>
<td>40.5±35.2</td>
</tr>
<tr>
<td>AHIR</td>
<td>40.7±41.6</td>
<td>11.2±12.0</td>
<td>53.2±43.3</td>
</tr>
</tbody>
</table>

* Sleep efficiency = total sleep time × 100/total recording time; percent stage X = time in stage X/total sleep time; Min O₂ = minimum oxygen saturation recorded. Data in all rows after the first two represent mean±SD.
† All variables listed were significantly different for AHI <10 and AHI ≥10 (χ² or t test, p≤0.0001).
² BMI data available on 413, 145, and 268 subjects only, in the three groups.
³ Min O₂ data available on 1,097, 327, and 770 subjects only, in the three groups.

Table 2—The Percent of Variance in MSLRT (100×R²) Explained by Each of Three Linear Regressions on AHI, AHIN, and AHIR

<table>
<thead>
<tr>
<th></th>
<th>% of Variance</th>
<th>% of Variance</th>
<th>% of Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p=</td>
<td>p=</td>
<td>p=</td>
</tr>
<tr>
<td>AHI</td>
<td>11.0±0.0001</td>
<td>3.1±0.0012</td>
<td>8.8±0.0001</td>
</tr>
<tr>
<td>AHIN</td>
<td>10.8±0.0001</td>
<td>2.3±0.0049</td>
<td>8.7±0.0001</td>
</tr>
<tr>
<td>AHIR</td>
<td>6.0±0.0001</td>
<td>0.2±0.4045</td>
<td>3.6±0.0001</td>
</tr>
</tbody>
</table>
between AHI and AHIR/AHIN on MSLRT became marginally significant (p=0.023 instead of p=0.10) but still explained virtually none of the variance in MSLRT (part $R^2$ for the interaction term=0.012).

**DISCUSSION**

This study shows that among patients with initially suspected or else confirmed sleep-disordered breathing, a higher AHI, AHIN, or AHIR is associated with a higher level of sleepiness as measured by the MSL. The strength of these associations is not large, and that for AHIR and MSL is particularly small. In comparison to AHIR, AHIN was more strongly related to MSL whether AHI was low (<10) or higher (≥10). The AHIN, which accounted for most of the association between AHI and MSL, retained an association with MSL after controlling for AHIR, whereas AHIR showed no association with MSL after controlling for AHIN. The lack of an independent association of AHIR with MSL was not due to inadequate power; these data from 1,146 patients represent, to our knowledge, the largest series of paired diagnostic polysomnograms and MSLTs reported to date.

The absence of a strong relation between AHI and MSL in our data was consistent with the findings of previous, smaller studies. However, our results were not consistent with those from the patients of Kass et al, all of whom had an AHI <10; in that study, the AHIR showed a relatively strong association with MSL and this association was stronger than that between AHI and MSL. Although not reported, AHIN can therefore be inferred to have had minimal, if any, relation to MSL.

We are not certain why we obtained different results from those reported by Kass et al. In that study, a large number of variables relative to the sample size were tested for a relation to MSL, raising the risk of spurious findings. Part of the study of Kass et al was done prospectively, but the report does not state whether investigators who scored the sleep studies were blind to the outcome variables. Our study was entirely retrospective, so knowledge of the study hypothesis could not have affected scoring. Differences between laboratories in procedures and scoring methods, especially in regard to hypopneas, sometimes account for different results. In our laboratory, patients were awakened at a relatively uniform time—7 AM—that may have curtailed the amount of REM sleep obtained and conceivably reduced our ability to detect a relation between the AHIR and MSL. The report by Kass et al does not state whether subjects were awakened in a similar manner. Kass et al also found an association between MSL and the number of transient arousals during REM, per hour of sleep; we were unable to test this relationship in our data because transient arousals had not been scored. However, Kass et al found that MSL correlated better with AHIR than with REM-related transient arousals, so our conclusions would most likely have been no different even if we had measured the latter (weaker) correlate.

The ratio of AHIR to AHIN in our subjects was significantly higher among subjects with lower overall AHI. This pattern makes detection of a relation between AHIR and MSL more likely when AHI <10 than when AHI is higher. Kass et al may have reached different conclusions about their patients with AHIN if they had controlled for overall AHI (or AHIN) while assessing the relation of AHIR to MSL.

Currently available data do not allow a confident theoretical prediction of whether apneas or other disturbances of REM sleep, in comparison to those of NREM sleep, would more effectively cause EDS. While some have suggested that such might be the case, others have presented evidence that slow-wave sleep, most prominent in NREM stages 3 and 4, is enhanced after acute sleep deprivation and preserved in the face of chronically curtailed sleep time, suggesting that deep NREM sleep may be most important to the restorative effect of sleep. Patients sleepy because of sleep-disordered breathing include those with apnea largely confined to REM sleep as well as those with upper airway resistance syndrome, which may be worse in NREM sleep than in REM sleep. Our data show that the ratio of the rates of apneic events in REM vs NREM sleep (AHIR/AHIP) has essentially no effect on the relation of overall AHI to sleepiness; the stronger association between AHIN and sleepiness, relative to that between AHIR and sleepiness, most likely arises because a much larger proportion of the night is spent in NREM sleep.

The absence of a strong association between AHI and MSL suggests the possibility that either we do not completely understand the physiology of sleepiness in patients with sleep-disordered breathing, or else the AHI and MSL, respectively, do not optimally assess the severity of sleep apnea and the degree of sleepiness. Although we cannot support the report by Kass et al that AHIR has particular relevance to sleepiness, we do share their speculation that increased upper airway resistance, measured by esophageal manometry during polysomnography, may help explain EDS in patients with lower AHI. In our laboratory, among 40 patients who had esophageal manometry and had an AHI <5, 13 were given a diagnosis of upper airway resistance syndrome (and subsequent unpublished data).
However, the maximal difference between end-inspiratory pressures while asleep and while awake explained little or none of the variation in MSL and several measures of sleep quality, including sleep efficiency, number of awakenings, number of entries to stage 1 sleep, and percent stage 1 sleep. The best way to characterize data recorded during esophageal manometry still remains undefined and might eventually allow better results. In addition, alternative ways to analyze MSLT data and modifications of the test itself deserve further investigation.26-28

REFERENCES

11 Aldrich MS, Channcey JB. Are morning headaches part of obstructive sleep apnea syndrome? Arch Intern Med 1990; 150:1265-67
14 Aldrich MS. The clinical spectrum of narcolepsy and idiopathic hypersomnia. Neurology 1996; 46:393-401
27 Pollak CF. How should the multiple sleep latency test be analyzed? Sleep 1997; 20:34-39